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☐ 1: Trends Mol Med 2002;8(4 Suppl):S55-61

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## Hsp90 inhibitors as novel cancer chemotherapeutic agents.

Neckers L.

Cell and Cancer Biology Branch, National Cancer Institute, National Institutes of Health, 9610 Medical Center Drive, Suite 300, Rockville, MD 20850, USA. len@helix.nih.gov

Heat shock protein 90 (Hsp90) is a molecular chaperone whose association is required for the stability and function of multiple mutated, chimeric and over-expressed signaling proteins that promote the growth and/or survival of cancer cells. Hsp90 client proteins include mutated p53, Bcr-Abl, Raf-1, Akt, ErbB2 and hypoxia-inducible factor 1 alpha (HIF-1 alpha). Hsp90 inhibitors, by interacting specifically with a single molecular target, cause the destabilization and eventual degradation of Hsp90 client proteins, and they have shown promising antitumor activity in preclinical model systems. One Hsp90 inhibitor, 17-allylaminogeldanamycin (17AAG), is currently in phase I clinical trial. Because of the chemoprotective activity of several proteins that are Hsp90 clients, the combination of an Hsp90 inhibitor with a standard chemotherapeutic agent could dramatically increase the in vivo efficacy of the therapeutic agent.

### Publication Types:

- Review
- Review, Tutorial

PMID: 11927289 [PubMed - indexed for MEDLINE]

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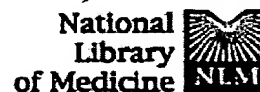
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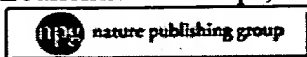
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☐ 1: Leukemia 2002 Apr;16(4):455-62

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## Hsp-90-associated oncoproteins: multiple targets of geldanamycin and its analogs.

Blagosklonny MV.

National Cancer Institute, NIH, Bethesda, MD 20892, USA.

Geldanamycin (GA), herbimycin A and radicicol bind heat-shock protein-90 (Hsp90) and destabilize its client proteins including v-Src, Bcr-Abl, Raf-1, ErbB2, some growth factor receptors and steroid receptors. Thus, Hsp90-active agents induce ubiquitination and proteasomal degradation of numerous oncoproteins. Depending on the cellular context, HSP90-active agents cause growth arrest, differentiation and apoptosis, or can prevent apoptosis. HSP-active agents are undergoing clinical trials. Like targets of most chemotherapeutics, Hsp90 is not a cancer-specific protein. By attacking a nonspecific target, HSP-90-active compounds still may preferentially kill certain tumor cells. How can this be achieved? How can therapeutic potentials be exploited? This article starts the discussion.

### Publication Types:

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